Important concept: antibodies neutralize/remove virus particles from the blood/resp/mucosa; CTL eliminate virus infected cells. ALL Viruses enter by Attachment, Penetration, Uncoating, Synthesis, Assembly, and Budding.

**DNA viruses:**

Essential and Nonessential genes, IE/E/L genes (IE reg cell and stim E which stim L), use DNA transcription/translation machinery in the nucleus then the cytoplasm, most encode their own DNA poly. **Sequential Gene Expression.**

**RNA (+)**

Identical to the mRNA and can be translated directly. Their VAP is a canyon on the icosahedral capsid. Produce poly protein after penetration/uncoating at CM. Polio virus requires a viral primer for the viral RNA dep RNA pol. This replication occurs in a membrane pocket open to the cytoplasm. Error prone and subject to DIP and recombination. NOTE: Make a provirion then VP0 splits to VP2,4. **Static Gene Expression**

**RNA (-) Mononega virus**

Helical nucleocapsids in an envelope; endocytosis pH dependent; intergenic regions with stop/start codons; monocistronic mRNA produced which attach to the RNA pol causing it to ignore the intergenic regions and replicate a complementary RNA template for RNA replication. M protein covers the inside of the CM and aids in the exocytosis of the virion. **Gradient Gene Expression**

**RNA Segmented Viruses**

Receptors (HA to sialic acid) mediate the attachment and penetration of the host cell. M1 is a matrix protein and M2 is a proton pump necessary for uncoating. RNA synthesis requires active host transcription and the virus needs to be in the nucleus. Assembly/budding is dependent on NA digestion of sugar moieties to which the viral particles are attached. NOTE: Influenza viruses cap steal from local mRNA in the nucleus.

**Double stranded RNA**

Again, HA mediates the attachment and the virus enters the cell as the first step of Early Phase. The second step of early phase is the transcription of mRNA (These are used for translation and also as a template for replication). The Late phase begins after transcription and the cell starts to produce structural proteins.

DIP- deleterious interfering particles: due to a failure in the packaging of a virus or the faulty replication. These lack the essential replication machinery and require a helper virus if they are to replicate. The helper virus is then partially inhibited as its machinery is being shared (AKA: Interference)

Mutation- RNA poly has 1 nucleotide mistake in every 10^3 or10^5. No proofreading capability or correcting machinery.

Recombination: like DIP, the RNA poly falls from one template with its nascent strand only to reattach to another template. This is **Copy choice.** The result is a fully functional and complete viral genome (rare in negative strand).

Reassortment: the result of faulty repackaging of virions where coinfected viruses can mix their segmented genome to produce a new virus.

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**Respiratory Viruses**

-transmitted by saliva droplets and can enter by merely contact with infected surface.

1. Rhino v.- Picorna (incubate 2-3 days) SX nasal, sneeze, sore throat, headache, cough, fever(+/-). Due to bradykinin causing blood engorgement of the nose (HYPEREMIC). Watch patients with asthma or chronic bronchitis. *No tests, vaccines or drugs*
2. Corona v.- Corona() SX upper respiratory infections in ONLY humans, NO fever, cough, sore throat. [SARS is unusual in that it can cause extensive pneumonia]. *RT-PCR, ELISA, Viral Culture; no vax; no real clear treatment except supportive care*
3. Adeno v.- Adeno () SX range from upper respiratory infections to gastro (40,41), conjunctiva, genital ulcer, pneumonia. Typical presentation is fever, sore throat, hurting eye and other people have the same thing (seen at camps and military). *IF, Cytopathic effect on human cell lines (cyncytia); oral encapsulated live-attenuated virus; supportive care.* NOTE: may be oncogenic?
4. Influenza v.- Orthomyxo (2-3 days) SX shivering, malaise, headache, fever (39C), myalgia and back ache. Upper respiratory infection that destroys the cilia of the upper airways leading to complications and secondary bacterial infections by staph. Mediated by IL6, IFN, TNF. *ELISA, IF; Nasal attenuated vax, inactivated vax; Rimantidine/amantadine, zanamivir/oseltamivir.* NOTE: may cause Reye’s syndrome in kids with aspirin.

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**Childhood Viruses (Mostly Paramyxo, but also Toga and Herpes)**

1. RSV- Paramyxo (5days to incubate and shed for 3 weeks) F gene is the protein mainly targeted by the immune response and it mediates membrane fusion independent of pH. Highly contagious especially in kids under 2 or elderly; smear show syncytia due to cell to cell fusion. SX significant rhinorrhea, WHEEZING, common cold of the lower resp, can cause peribronchial infiltration and interstitial pneumonia. *Indirect IF, culture; no vax; supportive care with Ribavirin. Can treat with passive immunization (premature babies) Palivizumab (monoclonal antibody against F).* NOTE biggest worry is for long term respiratory problems.
2. PIV- Paramyxo 4 types () most likely to infect people under the age of five and can be reoccurring. SX most often boys with croup. *Nebulizing steam helps allow the patient to cough out phlegm to prevent 2ndary bacterial infection.*
3. Measles- Paramyxo (prodrome is 2-3 days then syndrome) one of the most infectious viruses known. SX maculopapular rash on face to the trunk and limbs. Initial symptoms of runny nose, cough, high fever (+40C) are the prodrome. Koplik spots (bluish/white spots on the mucosa of the mouth) are diagnostic. Enter from the sight of infection to the lymph nodes and then throughout the body in the blood stream (VIREMIA). Cellular immune response mediated by the CTL and the virus shed in any body fluid. Epithelium and the lymph nodes show syncytia. *ELISA to determine antibody titers. Live attenuated vax available for kids.* NOTE: passive antibody protection but can cause croup, bronchitis, conjunctivitis, otitis media (2ndary) and Giant Cell Pneumonia in the immunosuppressed.
   1. SSPE subacute sclerosing panencephalitis can develop years later and is fatal. Causes demyelination and neural degeneration due to a hypermutated measles virus spreading to the brain
4. Mumps- paramyxo (2-3 weeks) this virus also has the F and G proteins and is shed in body fluids including the urine. Portal of entry is the respiratory tract. SX generalized malaise with fever. Within 24 hours of onset of symptoms, swollen parotid glands. MAY LEAD TO STERILITY due to orchitis. Can also cause meningitis and encephalitis. *Monkey cells to culture for IgM, ELISA; live attenuated vax, supportive care during the acute phase viremia*
5. Rubella- Toga similar to Flavi but more pleomorphic (2-3weeks) enters via respiratory route. SX with initial swelling of lymph nodes followed by a rash 1-2 days later. Low fever (around 37.xC). *ELISA for IgG. Use live attenuated vax.* NOTE: disease may cause encephalitis in children. Often causes poly arthritis in adults (especially women)
   1. Congenital Rubella: if mother contracts during first month = 100% mortality of fetus. Past that time leads to the syndrome of low birth weight, CVD/CNS impairment, liver enlarged, bone problems, diabetes, MR. (similar to HSV, CMV, toxoplasmosis)
6. New comer viruses are:
   1. 2001 Human metapneumovirus (paramyxo)
   2. 2005 Human Boca virus (parvo)

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**GI Viruses**

- must be capable of surviving the pH, bile salts, mucus; some attack the enterocytes while others attack the crypt cells. GI infection is the 2nd major cause of infectious morbidity.

- cause: Acute Viral Gastroenteritis (AVG), Opportunistic infection (think about HIV), Nonenteropathogenic viruses

AVG: (1-3days) fecal oral spread, abrupt onset vomiting and diarrhea, low grade fever and major concern is dehydration

1. Rota v.- Reo (1-3) person to person transmission, f-o, or contaminated food. Immunity governed by IgA. 90% of humans infected by age 3. 7 types with types ABC infecting humans most commonly under the age of 2. A is the most common while B is in the world and C is in Asia.  *Immune EM with IgA antibodies, RT-PCR; vax for kids shows 74% decrease in infection with 98% decrease in severe cases.*
2. Adeno 40,41- Adeno (1-3) target infants and can cause involution of the small intestine. Peyer’s patch is the target of the virus. *ELISA and PCR….*
3. Calici (Noro and Sapo)- Calici (1-3) cause vomiting and diarrhea in all populations across all age groups. Usually due to a contamination or aerosol from projectile vomiting. Virus targets brush border and impairs proper nutrient and water absorption. *ELISA, no vax, supportive therapy*
4. Astrovirus: naked, icosahedral, (+) ssRNA. Diarrhea in children in the winter. *ELISA*

Nonenteropathogenic viruses: just use the gut to replicate and then leave. Most are inapparent but others cause upper respiratory infections or viremia leading to myocarditis or meningitis. Most are Picorna viruses that have two Geni: Enterovirus (37⁰C) and Rhinovirus (33⁰C). Enteroviruses are discussed here:

1. Polio- enterovirus of Picorna with three subtypes (-) infect laryngeal lymphoid cells. Some of the viruses replicating in the enterocytes of the intestinal tract can enter the blood stream and travel to other organs to replicate (PRIMARY VIREMIA). Once the virions are released from these organs, the travel through the blood to the lymphocytes (SECONDARY VIREMIA). The higher the virion count the increased likelihood of meningitis as the virus crosses the BBB and attaches to the polio virus receptor on neurons. 90% asymptomatic, 10% have viral meningitis, 1% of infections lead to paralytic poliomyelitis (Asymmetric flaccid paralysis or bulbar polio with paralysis of cranial nerves). *Live virus orally or the killed virus IPV.*
   1. Post-polio syndrome- years later, some people show weakness or resurgence of symptoms from previous infection with polio
   2. Vaccine Associated Paralytic Poliomyelitis- a small percentage of the vaccinated people ended up contracting polio (2/1million)
2. Coxsackie- enterovirus (-) distinguished from polio by its specific antibody and by pathology.
   1. A has 23 types and causes herpangina, hand, foot and mouth disease (vesicle formation in all these areas). Type 16 can cause congenital heart disease and aseptic meningitis
   2. B has 6 serotypes and causes pleurodynia (epidemic myalgia), acute infectious myocarditis and pericarditis
3. ECHO- enterovirus() like cosackie but generally milder
4. Enterovirus 68,69,70, 71- 70 leads to acute hemorrhagic conjunctivitis; 71 causes hand, foot, mouth disease in children and some brain infections that can be fatal (mostly Asia)

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**Parvo Viruses**

-Unique because of the ssDNA. This DNA folds back on itself with hairpin turns to serve as DNA primers.

1. AAV (Adenovirus-associated-virus)- no known human disease and has lost its replication machinery. Needs the Adenovirus as a helper cell
2. Boca virus- acute respiratory infections (ARI) in infants and children during the winter months
3. Human erythro v. (B19)- parvo (-) worldwide and common infectious agent in humans. Immunocompromised kids develop erythema infectiosum (Slapped cheek syndrome or Fifth’s), innocuous rash, mild fever. Targets RBC precursors and can cause a temporary decrease in production.
   1. Fifth’s disease- slapped cheeks, lacy rash, slight fever for kids (resolves 7-10days)
   2. Polyarthropathy- develop acute, symmetric poly arthritis in adults that looks like RA
   3. Transient Aplastic Crisis (TAC)- individuals with poor RBC production (thalassemia, sickle cell…) show a self-limiting but acute anemia. Also people with low iron, hemorrhage or bone mare transplant can also show TAC
   4. Pure Red Cell Aplasia/Chronic Anemia- shown when the patient cannot produce antibodies to neutralize the B19 infection. VERY SERIOUS
   5. Hydrop Fetalis- congenital anemia due to mother with B19
      1. *NOTE: PCR, ELISA to detect antibodies; administer neutralizing antibodies*

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**PaPova Viruses (tumor viruses also included)**

-polyoma virus in mice and SV40 in monkeys were the first viruses to show that viruses can trigger the local tissue to become cancerous. The p52 antigen is a tumor suppressor gene by repairing DNA, triggering apoptosis in troublesome cells, and activates repressor genes for the cell cycle. The Early region in the PaPova viruses causes the formation of a protein product called Large T or small T. This large T is the spliced product and binds to host p53. It induces the cell to proliferate if in G0, complexes with DNA pol/p53/RB, activates viral DNA synthesis, binds Ori, turns on/off late/early genes.

1. JC virus- polyoma virus that is a mutated measles that causes progressive multifocal leukoencephalopathy (PML)
2. BK virus- polyoma from transplant patients. Initially minor respiratory infection where becomes persistent in the kidneys. After stress, it reactivates causing hemorrhagic cystitis

About 80% of people have been infected with these as kids and immunosuppression can reactivate these. *Diagnose with PCR for genome DNA and ELISA for antibody*

-papilloma virus (HPV)- PaPova ()causes warts or verrucae and are associated with epithelial cancers. HPV attaches to basement endothelial cells where the virus uncoats and starts the early phase protein production. As the keratinocytes differentiate, the virus will enter late stage. The dead keratinocyte is sloughed and the progeny virions released with the dead cell. Condyloma (anogenital warts) can develop as well as Epidermodysplasia verruciformis (precancerous). *To diagnose, isolate DNA, radiolabeled cloning with cross hybridization or direct sequencing looking for a match*

1. 6 and 11 are precancerous HPV
2. 16,18,31 are invasive carcinomas of the cervix
   1. *GARDASIL for 6,11,16,18 that are empty capsids that have been generated and protect 70% from cancer and 90% from warts*

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**Pox Viruses**

-most complex viruses, have a core with lateral bodies and carry everything they need to infect the host and replicate in the cytoplasm. They also encode for decoy molecules like TNF receptor. Four families exist: Ortho, Para, Yata, Mollusci

1. Variola- small pox Ortho class (2 weeks) caused by inhalation or contact. Infection of the mouth and lungs occurs without symptoms after which the macrophages carry the virus through the body. SX flu like symptoms with fever (+40C). As the fever breaks the oral enanthems emerge. Over the next three days the cell associated virus is localized to the dermal vasculature where exanthems present themselves as smooth pustules that are filled with little hard balls (shotty). Pustules crust then scab over the next two weeks. Biggest concern is the dehydration, sloughing skin, temperature rise. Can show symptoms of vomiting and diarrhea. Confers lifelong immunity if survive (Variola major 30% mortality, Variola minor 1%).
2. Vaccinia- attenuated and less virulent form of small pox
3. Monkey pox- similar to cow pox but only in Africa and low human to human transfer
4. Cow/Psuedocow/Orf are all Ortho and Para…. Caused by livestock transferring their virus
5. Molluscum- multiple small nodular lesions with packets that cause conjunctivitis and keratitis.

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**Herpes Viruses**

Capable of lytic, persistent, latent infection. Mostly carried by humans. Genomes code for proteins that alter the immune response. Three types alpha which attack the neurons, beta targeting tcells and gamma targeting b cells. The dsDNA has two covalently linked regions called unique long and unique short regions.

1. HHV1/2- HSV1/2 both infect humans where 1 is above the waist and can cause encephalitis(95% of viral encephalitis) and 2 is below the waist and can cause meningitis as well as vomiting and diarrhea. Rely on Thymidine Kinase to generate dNTP. Budding occurs at the nuclear membrane and virions stored in ER till cell lyses. Can be reactivated by stress. SX flu like symptoms, oral/genital blisters (also pharyngitis, keratoconjunctivitis, whitlow, gladiatorum). Involves epithelium, spreads to neurons and stays in ganglion. Mediated by CTL but antibodies may also help. Can have reoccurrence and reactivation. Latex helps to protect but not bullet proof. *Tzanck smear for ballooned cells with cowdry inclusions, EM, IF, PCR; no vax; treat with acyclovir to inhibit TK. If no good use Vala/Pen/Fam-ciclovir. Ara-C helps but less effective.*
2. Varicella zoster- HHV 3(2weeks) similar to HSV but slower, smaller, infect fewer cell types. One of the five classic exanthems. Enters by way of Resp system and cell to cell transfer. Goes to organs->skin->neurons/ganglia. SX Maculopapular rash on trunk and then limbs, fever. Develop lesion followed by vesicle which becomes pustular->crusty->scab. Lesions at all stages can be observed (unlike small pox). Reactivation of the infection causes zoster which leads to dermatomal display with painful vesicles forming along infected nerves. *Tzanck smear with cowdry inclusions in syncytia, ELISA, PCR;vax;supportive treatment.* NOTE: can cause dissemination to lungs, brain, liver in elderly or immunocomp. Older patients can develop posttherpetic neuralgia.
3. Herpes B- from monkeys and occasionally infects humans. Bite can be fatal by triggering encephalomyelitis
4. Cytomegalovirus (CMV)- beta HHV5() most common adult infection. Can cause congenital defects. Increasingly prevalent in immunocompromised where it establishes opportunistic infections. 1% infected…. 10% show symptoms. Sexually transmitted disease. Immunocompromised at a high risk of pneumonia, retinitis and colitis. SX usually just a fever, cough, short of breath as an adult. Most are inapparent with persistent/latent in Tcells/macrophages. *“Owl’s eye inclusions” on histology, IF, PCR, ELISA; no vax; Ganciclover and vanciclovir, cidofovir, foscarnet all used to treat by attacking CMV kinase/acting as a cytidine analog or inhibiting DNA pol*
5. Herpes 6&7- exanthem subitum/rosella with short fever and may have a rash. Mono and swollen lymphnodes.
6. Epstein Barr Virus- HHV 4 with A and B types () Saliva transmission and primary issue is the virus’s ability to immortalize cells. Markers are EA, EBNA, VCA, MA. SX infectious mononucleosis with fatigue 6-8weeks , swollen lymphnodes, fever for two weeks, exudative pharyngitis, spleno- hepato- megaly. Can be an issue with lymphoproliferative diseases causing extremely low immunity and mouth lesions. Virus infects the lymphocytes and produce an inappropriate immune response from an IL10 analog. Can cause Lymphoma. Lymphocytosis and malaise are due to Tcell activation/proliferation and they appear “Downy” and can be 10-80% of WBCC. *Use lymphocyte counts, heterophile antibody, PCR and cell antigens. No vax, no treat.* NOTE: long term can cause something similar to chronic fatigue syndrome and neurocomplications
7. Kaposi Sarcoma-associated Herpes Virus- HHV 8 () can cause sarcomas and other proliferative disorders (lymphoma, castlemans). Associated with HIV but also with older mediteranean men. Sexually transmitted; when reactivated can cause immortalization of endothelial cells and lung infection. *Use Symptoms, PCR and serology to diagnose.*

**Zoonoses**